HETEROCYCLES, Vol. 87, No. 6, 2013, pp. 1241 - 1247. © 2013 The Japan Institute of Heterocyclic Chemistry
Received, 16th March, 2013, Accepted, 26th April, 2013, Published online, 13th May, 2013
DOI: 10.3987/COM-13-12708

SYNTHESIS OF INDOLES: SULFUR-ASSISTED REACTION OF 2-NITROSTILBENES WITH CARBON MONOXIDE

Rui Umeda, Yuuta Nishimoto, Tsukasa Mashino, and Yutaka Nishiyama*

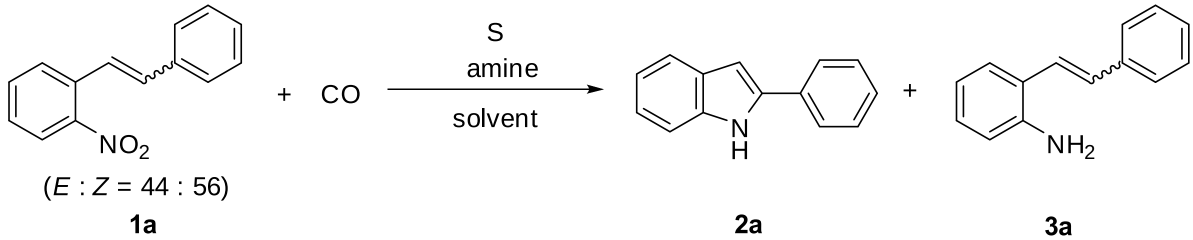
Department of Chemistry and Materials Engineering, Faculty of Chemistry, Materials and Bioengineering, Kansai University, Suita, Osaka 564-8680, Japan
E-mail: nishiya@kansai-u.ac.jp

Abstract – When 2-nitrostilbenes were treated with carbon monoxide in the presence of elemental sulfur, the reductive *N*-heterocyclization of the 2-nitrostilbenes smoothly proceeded to give the corresponding indoles in moderate to good yields.

The indole ring system is one of the most ubiquitous heterocyclics in nature,[1] and the development of a synthetic method of the indole system has received considerable attention in the industrial, agricultural, and pharmaceutical chemistries.[2] For well over a hundred years, numerous synthetic methods of indoles including the well-established methods such as the Fischer,[3] Madelung,[4] Leimgruber-Batcho,[5] Bartoli,[6] Bischler-Mohlan,[7] Hametsberger-Knittel,[8] Larock,[9] Reissert,[10] Gassman,[11] and Sundberg[12] indol syntheses have been disclosed. As the other attractive applications on the synthesis of indoles, there are some reports on the metal-catalyzed cyclization of 2-amino substituted arenes.[13] Alternatively, transition metal-catalyzed reductive *N*-heterocyclization of 2-nitrostyrenes with carbon monoxide as a reducing agent has been developed for the synthesis of indoles.[14,15] As another approach for the method using reductive *N*-heterocyclization, we have recently shown that selenium, non transition metal, was an efficient catalyst for the synthesis of indoles by the reductive cyclization of 2-nitro substituted styrenes with carbon monoxide.[16] However, for these methods using carbon monoxide as a reducing agent, there are some disadvantages such as the use of expensive metals, unstable catalysts in air or moisture, and their toxicity. To solve these disadvantages, we examined the use of sulfur for the reaction of 2-nitro substituted stilbenes with carbon monoxide and found that the reductive *N*-heterocyclization of these compounds proceeded to give the corresponding indoles in moderate to good yields.

To determine the optimized reaction conditions, 2-nitrostilbene (**1a**) was allowed to react with carbon monoxide in the presence of sulfur under various reaction conditions, and these results are shown in Table 1. When **1a** was treated with carbon monoxide (30 atm) in the presence of sulfur and excess amounts of triethylamine in DMF solvent at 120 °C for 24 h, the reductive *N*-heterocyclization of **1a** efficiently occurred to give 2-phenylindole (**2a**) in 59% yield along with the formation of 2-aminostilbene (**3a**) (17%) (entry 1). In the cases of DMA and acetonitrile, **2a** was formed in 56 and 39% yields, respectively (entries 2 and 3). The use of other solvents, such as THF and benzene, caused a distinct decrease in the yield of **2a** (entries 4 and 5). For the reaction using *N*-methylpyrrolidine, DBN and DBU instead of triethylamine as a base, the yield of **2a** was decreased (entries 6-8). At a lower reaction temperature (80 °C), the yield of **2a** was low (entry 10). The yield of **2a** was improved by elevating the reaction temperature (150 °C) (entry 9). In order to determine the possible catalytic use of sulfur, **1a** was treated with carbon monoxide in the presence of a catalytic amount of sulfur (20 mol%). 2-Phenylindole (**2a**) was formed in 200% yield based on sulfur.

Table 1. The Sulfur-Assisted Reaction of 2-Nitrostilbene with Carbon Monoxide under Various Reaction Conditions[a)]

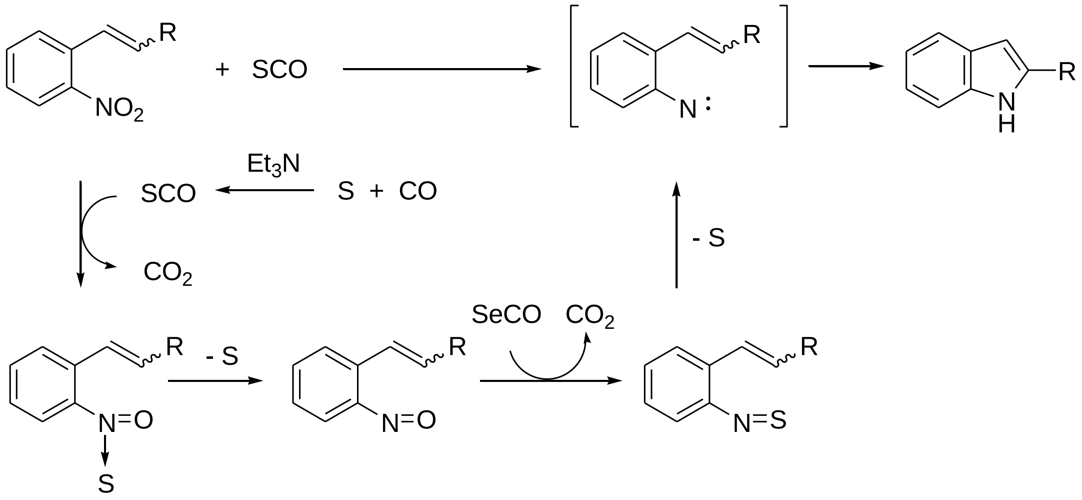


Entry	Amine	Solvent	Temp. / °C	Time / h	Yield / %[b)]	
					2a	**3a**
1	Et_3N	DMF	120	24	59	17
2	Et_3N	DMA	120	24	56	13
3	Et_3N	CH_3CN	120	24	39	5
4	Et_3N	THF	120	24	0	0
5	Et_3N	benzene	120	24	0	0
6		DMF	120	24	7	1
7	DBN	DMF	120	24	7	35
8	DBU	DMF	120	24	11	42
9	Et_3N	DMF	150	24	83 (68)	13
10	Et_3N	DMF	80	24	7	1

a) Reaction conditions: 2-nitrostilbene (0.5 mmol), sulfur (0.5 mmol), amine (10 mmol) and solvent (5 mL) under CO (30 atm). b) GLC yields. The number in parenthesis shows the isolated yield.

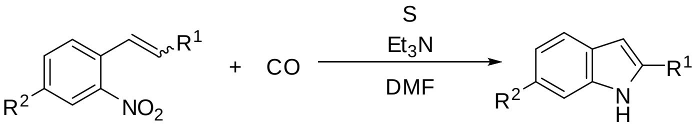
To determine the applicability of the sulfur-assisted reductive *N*-heterocyclization of 2-nitrostilbene derivatives with carbon monoxide, a variety of 2-nitro substituted stilbenes was allowed to react with carbon monoxide in the presence of a stoichiometric amount of sulfur using triethylamine as the base and DMF as the solvent. These results are shown in Table 2.[17] In the case of 1-(2-nitrostyryl)-4-methylbenzene, 1-(2-nitrostyryl)-3-methylbenzene, and 1-(2-nitrostyryl)-3-methoxybenzene having electron donating groups, the reductive *N*-heterocyclization efficiently proceeded to form the corresponding indoles, **2b-c** and **2e**, in 86, 82 and 85%, respectively (entries 1, 2, and 4). Similarly, 1-(2-nitrostyryl)-4-chlorobenzene and 1-(2-nitrostyryl)-4-trifluoromethylbenzene, in which electron withdrawing groups were substituted on the aromatic ring, were reductive *N*-heterocyclized to give the corresponding 2-aryl substituted indoles **2f-g** in good yields (entries 5 and 6). In the case of 1-(2-nitrostyryl)-2-methylbenzene, which has a sterically hindered group, the yield of **2d** slightly decreased (entry 3). The reductive *N*-heterocyclization of 1-(4-methoxy-2-nitrostyryl)benzene with carbon monoxide also occurred to produce **2h** in 43% yield (entry 7). 2-Methylindole (**2i**) was also prepared by the sulfur-assisted reductive *N*-heterocyclization with carbon monoxide (entry 8).

Although the reaction pathway for the preparation of the indoles by the reaction of 2-nitrostilbenes with carbon monoxide in the presence of sulfur has not been fully clarified, one of the plausible reaction pathways is shown in Scheme 1. Miyata and Sonoda et al. reported the sulfur-assisted synthesis of benzimidazolones, benzoxazolones, and benzothiazolones by the reaction of *o*-substituted nitrobenzenes with carbon monoxide in the presence of water.[18] They proposed that the generation of carbonyl sulfide by the reaction of sulfur and carbon monoxide in the presence of a tertiary amine was the initial step of the reaction. Thus, we propose that the reaction starts with the deoxygenation of the nitro group with SCO, which was generated by the elemental sulfur and carbon monoxide in the presence of the tertiary amine, forming the corresponding short-lived nitrene or nitrenoid species. The intramolecular insertion of the nitrene or nitrenoid species into the vinylic C-H bond efficiently proceeded to produce the indoles.

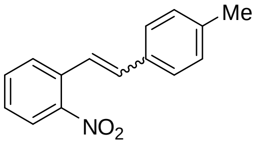
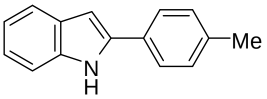
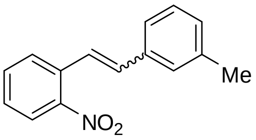
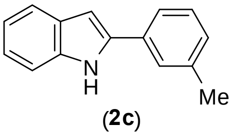
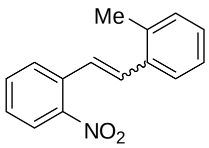
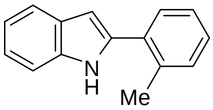
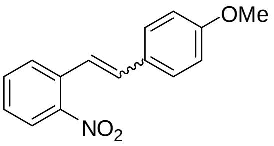
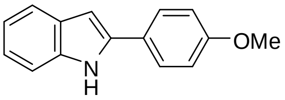
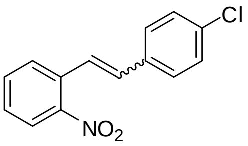
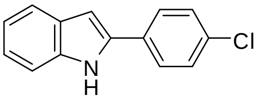
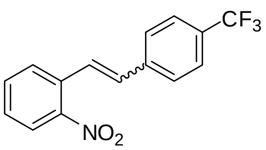
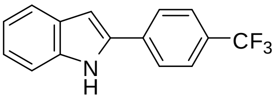
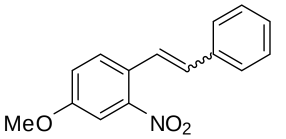
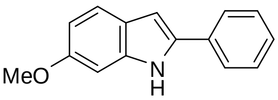
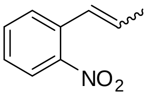
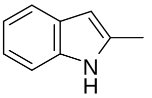


Scheme 1. A Plausible Reaction Path

Table 2. Synthesis of Various Indoles$^{a)}$



2

Entry	Substrate	Product	Yield / %$^{b)}$
1	 (*E* : *Z* = 50 : 50)	 (**2b**)	86
2	 (*E* : *Z* = 50 : 50)	 (**2c**)	82
3	 (*E* : *Z* = 50 : 50)	 (**2d**)	60
4	 (*E* : *Z* = 53 : 47)	 (**2e**)	85
5	 (*E* : *Z* = 63 : 37)	 (**2f**)	90
6	 (*E* : *Z* = 75 : 25)	 (**2g**)	82
7	 (*E* : *Z* = 47 : 53)	 (**2h**)	(43)
8	 (*E* : *Z* = 28 : 72)	 (**2i**)	(38)

a) Reaction conditions: 2-nitrostyrenes (0.5 mmol), sulfur (0.5 mmol), Et_3N (10 mmol) and DMF (5 mL) under CO (30 atm) at 150 °C for 24 h. b) GLC yields. The numbers in parentheses show the isolated yields.

In summary, we have succeeded in the synthesis of indoles via the sulfur-assisted reductive *N*-heterocyclization of 2-nitrostilbenes with carbon monoxide using sulfur.

ACKNOWLEDGMENT

This work was financially supported in part by a Grant-in-Aid for Science Research on Priority Area and Strategic Project to Support the Formation of Research Bases at Private University from the Ministry of Education, Culture Sports, and Science and Technology of Japan.

REFERENCES AND NOTES

1. (a) 'The Chemistry of the Alkaloids,' ed. by S. W. Pelletier, Van Nostrand Reinhold Company: New York, 1970, Chapter 9 and 10; (b) R. J. Sundberg, 'The Chemistry of Indoles,' Academic Press: New York, 1970; (c) 'Comprehensive Heterocyclic Chemistry,' ed. by A. R. Katritzky and C. W. Rees, Pergamon: Oxford, 1984, Vol. 4; (d) M. R. Grimmett, 'Comprehensive Organic Chemistry,' ed. by S. D. Barton and W. D. Ollis, Pergamon Press; Oxford, 1979, Vol. 4, p 357; (e) L. C. Behr, 'The Chemistry of Heterocyclic Compounds,' ed. by R. H. Wiley, Interscience Publisher: New York, 1967, Part 3, p 289; (f) R. J. Sundberg, 'Indoles,' Academic Press: London, 1996.
2. For recent reviews: (a) G. W. Gribble, *Contemp. Org. Synth.*, 1994, **1**, 145; (b) L. S. Hegedus, *Angew. Chem. Int. Ed.*, 1988, **27**, 1113; (c) T. Sakamoto, Y. Kondo, and H. Yamanaka, *Heterocycles*, 1988, **53**, 1170; (d) C. W. Gribble, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1045 and references therein.
3. E. Fischer and F. Jourdan, *Chem. Ber.*, 1883, **16**, 2241.
4. W. Madelung, *Chem. Ber.*, 1912, **45**, 1128.
5. A. D. Batcho and W. Leimgruber, *Org. Syn.*, 1985, **63**, 214.
6. G. Bartoli, G. Palmieri, M. Bosco, and R. Dalpozzo, *Tetrahedron Lett.*, 1989, **30**, 2129.
7. A. Bischler, *Chem. Ber.*, 1892, **25**, 2960.
8. H. Hemetsberger and D. Knittel, *Monatsh. Chem.*, 1972, **103**, 194.
9. R. C. Larock, E. K. Yum, and M. D. Refvik, *J. Org. Chem.*, 1998, **63**, 7652.
10. A. Reissert, *Chem. Ber.*, 1897, **30**, 1030.
11. P. G. Gassman, G. Gruetzmacher, and T. J. van Bergen, *J. Am. Chem. Soc.*, 1973, **95**, 6508.
12. R. J. Sundberg, *J. Org. Chem.*, 1965, **30**, 3604.
13. For recent reviews: (a) M. Platon, R. Amardeil, L. Djakovitch, and J.-C. Hierso, *Chem. Soc. Rev.*, 2012, **41**, 3929; (b) K. Sapeta, T. P. Lebold, and M. A. Kerr, *Synlett*, 2011, 1495; (c) G. Palmisano, A. Penoni, M. Sisti, F. Tibiletti, S. Tollari, and K. M. Nicholas, *Curr. Org. Chem.*, 2010, **14**, 2409; (d) J. Barluenga, F. Rodriguez, and F. J. Fananas, *Chem. Asian J.*, 2009, **4**, 1036; (e) S. Cacchi and

G. Fabrizi, *Chem. Rev.*, 2005, **105**, 2873.

14. (a) C. Crotti, S. Cenini, B. Rindone, S. Tollari, and F. Demartin, *J. Chem. Soc., Chem. Commun.*, 1986, 784; (b) C. Crotti, S. Cenini, R. Todeschini, S. Tollari, and F. Demartin, *J. Chem. Soc., Faraday Trans.*, 1991, **87**, 2811; (c) K. Okuro, J. Gurnham, and H. Alper, *J. Org. Chem.*, 2011, **76**, 4715; (d) S. R. Banini, M. R. Turner, M. M. Cummings, and B. C. G. Söderberg, *Tetrahedron*, 2011, **67**, 3603; (e) R. W. Clawson, Jr., C. A. Dacko, R. E. Deavers, III, N. G. Akhmedov, and B. C. G. Söderberg, *Tetrahedron*, 2009, **65**, 8786; (f) B. C. G. Söderberg, S. R. Banini, M. R. Tunner, A. R. Minter, and K. Arrington, *Synthesis*, 2008, **6**, 903; (g) B. C. Söderberg, A. C. Chisnell, S. N. O'Neil, and J. A. Shriver, *J. Org. Chem.*, 1999, **64**, 9731; (h) B. C. Söderberg, S. R. Rector, and S. N. O'Neil, *Tetrahedron Lett.*, 1999, **40**, 3657; (i) B. C. Söderberg and J. A. Shriver, *J. Org. Chem.*, 1997, **62**, 5838; (j) M. Akazome, T. Kondo, and Y. Watanabe, *J. Org. Chem.*, 1994, **59**, 3375; (k) S. Tollari, S. Cenini, C. Crotti, and E. Gianella, *J. Mol. Catal.*, 1994, **87**, 203; (l) M. Akazome, T. Kondo, and Y. Watanabe, *Chem. Lett.*, 1992, 769.

15. Recently, the protocol for the synthesis of indoles by the electrochemical reduction of 2-nitrostilbenes has been developed. See: P. Du, J. L. Brogner, and D. G. Peters, *Org. Lett.*, 2011, **13**, 4072.

16. Y. Nishiyama, R. Maema, K. Ohno, M. Hirose, and N. Sonoda, *Tetrahedron Lett.*, 1999, **40**, 5717.

17. **Experimental Procedure**

General

The FT-IR spectra were recorded by a JASCO FT/IR-4100 instrument. The ^{1}H-NMR spectra were recorded at 270 or 400 MHz and the ^{13}C-NMR spectra at 67.5 or 100 MHz by a JEOL, JNM-EX-270 or JEOL JNM-AL400. Chemical shifts were reported in ppm relative to tetramethylsilane or residual solvent as the internal standard. The GLC mass spectral analyses were performed by a Shimadozu GCMS-QP5050A with CBP-M25-025. The mass spectral analyses were performed by a JEOL JMS-700 spectrometer for the EI and FAB ionization. Preparative HPLC separation was undertaken using a JAI LC-908 chromatograph equipped 600 mm x 20 mm JAIGEL-1H and 2H GPC columns and $CHCl_3$ as the eluent.

Reagents

The sulfur and carbon monoxide were commercially available and were used without further purification. The 2-nitrostilbenes were synthesized by the Wittig reaction. All other chemical agents were commercially obtained and purified by distillation.

General Procedure for Sulfur-Assisted Reaction of 2-Nitrostilbens with Carbon Monoxide

To an autoclave, 2-nitrostilbene (0.5 mmol), sulfur (16 mg, 0.5 mmol), and triethylamine (101 mg, 10 mmol), was added to DMF (5 mL). The apparatus was then flushed several times with carbon monoxide and fully charged with carbon monoxide (30 atm) at room temperature. The reaction was carried out at 150 °C for 24 h. The reaction apparatus was then cooled to room temperature. After the evacuation of the excess carbon monoxide, the deposited sulfur and salt were filtered off and the solution was then extracted with diisopropyl ether. The organic layer was dried over $MgSO_4$. The resulting mixture was filtered, and the filtrate was concentrated. Purification of the residue by silica gel column chromatography afforded the indoles. The structures of the products were assigned by their ^1H and ^{13}C-NMR, and mass spectra. The product was characterized by comparing its spectral data with those of an authentic sample or previous reports on **2a-h**,[19] **2i**,[20] and **3a**.[20]

18. (a) T. Miyata, N. Kambe, S. Murai, N. Sonoda, O. Nishiguchi, and T. Hirashima, *Nippon Kagakukaishi*, 1987, 1332; (b) T. Miyata, T. Mizuno, Y. Nagahama, O. Nishiguchi, T. Hirashima, N. Sonoda, *Heteroatom Chem.*, 1991, **2**, 473.
19. S.-D. Yang, C.-L. Sun, Z. Fang, B.-J. Li, Y.-Z. Li, and Z.-J. Shi, *Angew. Chem. Int. Ed.*, 2007, **47**, 1473.
20. M. Shen, B. E. Leslie, and T. G. Driver, *Angew. Chem. Int. Ed.*, 2007, **47**, 5056.